

# Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections

Jason Tan Christine H. Smith MBBS Ran D. Goldman MD FRCPC

## Abstract

**Question** I have heard about children who have tic disorders that seem to be exacerbated by group A  $\beta$ -hemolytic streptococcal infection. Should children presenting with this phenomenon receive treatment with antibiotics, receive prophylactic treatment, or use immunomodulators to treat the symptoms?

**Answer** Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) constitute a condition that includes neuropsychiatric symptoms, mainly obsessive-compulsive disorder or tic disorders, temporally associated with an immune-mediated response to streptococcal infections. The actual existence of PANDAS as a unique clinical entity is still up for debate, as a temporal association between group A  $\beta$ -hemolytic streptococcal infections and symptom exacerbations has been difficult to prove thus far. Based on only a few studies, positive results have been found using antibiotic prophylaxis and immunomodulatory therapy in children with PANDAS. At this time, however, evidence does not support a recommendation for long-term antibiotic prophylaxis or immunomodulatory therapy.

## Affections neuropsychiatriques autoimmunes pédiatriques associées aux infections à streptocoques

### Résumé

**Question** J'ai entendu parler d'enfants ayant des tics qui semblent exacerbés par une infection à streptocoques  $\beta$ -hémolytiques du groupe A. Les enfants qui présentent un tel phénomène devraient-ils recevoir un traitement aux antibiotiques, un traitement prophylactique ou utiliser des immunomodulateurs pour traiter les symptômes?

**Réponse** Les affections neuropsychiatriques autoimmunes pédiatriques associées aux infections à streptocoques (PANDAS) sont un problème qui comporte des symptômes neuropsychiatriques, principalement un trouble obsessionnel-compulsif ou des tics, temporellement reliés à une réaction à médiation immunitaire à des infections à streptocoques. L'existence réelle des PANDAS en tant qu'entité clinique particulière est encore sujette à controverse, car il a été difficile à prouver jusqu'à présent une association temporelle entre les infections à streptocoques  $\beta$ -hémolytiques du groupe A et les exacerbations des symptômes. En se fondant sur quelques études seulement, on peut dire que des résultats positifs ont été observés à la suite d'une prophylaxie aux antibiotiques et d'une thérapie avec des immunomodulateurs chez les enfants présentant une PANDAS. À l'heure actuelle, cependant, les données scientifiques n'appuient pas la recommandation d'une prophylaxie aux antibiotiques ou d'une thérapie aux immunomodulateurs à long terme.

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) constitute a unique phenomenon prominently associated with obsessive-compulsive disorder (OCD) and tic disorder in children.<sup>1</sup> The current diagnostic criteria for PANDAS are as follows:

- presence of OCD or a tic disorder;
- prepubertal or pediatric (usually between 2 and 12 years of age) onset of symptom exacerbations;
- an episodic course of symptom severity and abrupt onset of symptoms;
- symptom association with group A  $\beta$ -hemolytic streptococcal (GABHS) infection; and

- association with neurologic abnormalities.<sup>1</sup>

Gabbay et al observed significant overdiagnosis of PANDAS among children in the community in the New York area, compared with a specialty centre ( $P < .03$ ), resulting in overuse of antibiotics and even immunomodulatory therapies (eg, plasma exchange or immunosuppression).<sup>2</sup> Only 63% of patients received the recommended therapy for their neuropsychiatric symptoms.<sup>2</sup>

In a case-controlled study of 40 matched children (cases with PANDAS matched to children with OCD or a chronic tic disorder but no known GABHS), only 5 of 64 exacerbations were associated (within 4 weeks) with a GABHS infection. All of these were in the

children with PANDAS. Most exacerbations (75%) were not associated with GABHS.<sup>3</sup> The authors from New York suggested that patients with PANDAS represented a subgroup of children with chronic tic disorders and OCD who might be vulnerable to GABHS infection as a precipitant of neuropsychiatric symptoms. Other infections might represent antecedent events associated with exacerbations.<sup>3</sup>

In a recent blinded, prospective, longitudinal study over 2 years, children with PANDAS were compared with children with Tourette syndrome or OCD without documented PANDAS.<sup>4</sup> There were no statistical differences in the numbers of clinical exacerbations or newly diagnosed GABHS infections between groups. In the PANDAS group, only in 12% (6 of 51) of suspected infections was a newly diagnosed GABHS infection documented. These findings add to the challenge of determining whether PANDAS actually exists.<sup>4</sup>

### Pathophysiology

The exact pathophysiology of PANDAS is still unknown, but the current hypothesis is that a GABHS infection results in an autoimmune-mediated process involving antineuronal antibodies.<sup>3,5</sup> It is likely that a spectrum of neurobehavioural disturbances, and not only Sydenham chorea (the neurologic sequela associated with acute rheumatic fever), are related to an immune-mediated pathophysiology.<sup>3</sup> The presence in PANDAS cases of circulating antineuronal antibodies, the increased prevalence of a B-cell surface marker that is associated with rheumatic fever, and the rapid clinical response to antibiotics and immunomodulatory therapy support this hypothesis.<sup>6</sup>

### Is PANDAS a unique entity?

Whether PANDAS is a unique clinical entity continues to be questioned.<sup>6</sup> As a result of the high incidence of GABHS infections in the pediatric population, the relationship between PANDAS and GABHS infections might be purely coincidental.<sup>3,7,8</sup> It has also been proposed that symptom exacerbations are brought on by stress resulting from the GABHS infection instead of being caused by an immune-mediated response. One study, in which serial serum samples from 12 patients with PANDAS were obtained before, during, and after symptom exacerbation, reported no correlation between clinical exacerbations and autoimmune markers.<sup>9</sup> Six of the 12 children had symptom exacerbations temporally associated with GABHS infection, while the other 6 did not.<sup>9</sup> Similarly, a study measuring anti-basal ganglia antibodies using enzyme-linked immunosorbent assay against basal ganglia from human caudate nucleus, putamen, and globus pallidus in 15 patients with PANDAS found no statistical differences in optical density readings for serum antibodies compared with

controls.<sup>10</sup> Additional research is required in order to better understand PANDAS before judging whether or not PANDAS is a unique clinical entity.<sup>3,5,11</sup>

### PANDAS therapy


Antibiotics are indicated for the treatment of documented GABHS infections regardless of the presence of neuropsychiatric symptoms.<sup>11</sup> Among 12 school-aged children with new-onset PANDAS, penicillin or cephalosporin (for 10 days) led to improvement in OCD symptoms in 5 to 21 days.<sup>12</sup>

As to prophylactic antibiotics, in one pilot, double-blind, balanced crossover study of 37 children with PANDAS, 250 mg of oral penicillin V twice daily or placebo was given to patients.<sup>13</sup> The rate of GABHS infection and the severity of symptoms between the 2 groups were not statistically different.<sup>13</sup> In a second study, 23 children aged 5 to 10 years took 250 mg of penicillin VK twice daily or 250 mg of azithromycin twice daily, once a week for 12 months. This resulted in a 96% decline in GABHS infections (50 to 2), and neuropsychiatric symptoms declined 61% (44 to 17).<sup>14</sup> The differences in infections and symptom exacerbations between the 2 groups were not statistically significant.<sup>14</sup>

### Immunomodulation

To date, one study has reported on immunomodulatory therapy for PANDAS.<sup>15</sup> Among the 30 children with PANDAS who were treated with immunomodulatory therapy (intravenous immunoglobulin and plasma exchange), OCD symptoms improved after both therapies, while tic symptoms improved only with plasma exchange.<sup>15</sup> While the results of the study seem promising, the authors advise that the use of immunomodulatory therapies will need further research before it can be recommended.<sup>15</sup>

### Conclusion

Without more knowledge about PANDAS, and definitive evidence linking GABHS infections to neuropsychiatric symptom exacerbations by way of immune-mediated processes, the diagnosis of PANDAS and the use of long-term antibiotic prophylaxis or any immunomodulatory therapies in place of or concomitantly with conventional therapies cannot be recommended.<sup>5,15,16</sup> 

#### Competing interests

None declared

#### Correspondence

Dr Ran D. Goldman, BC Children's Hospital, Department of Pediatrics, Room K4-226, Ambulatory Care Bldg, 4480 Oak St, Vancouver, BC V6H 3V4; telephone 604 875-2345, extension 7333; fax 604 875-2414; e-mail [rgoldman@cw.bc.ca](mailto:rgoldman@cw.bc.ca)

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